Clinical Performance of a Multiparametric MRI-based Post Concussive Syndrome Index

Steven P Meyers (✉ steven_meyers@urmc.rochester.edu)  
University of Rochester School of Medicine and Dentistry  
https://orcid.org/0000-0003-4192-6486

Adnan Hirad  
University of Rochester School of Medicine and Dentistry

Patricia Gonzalez  
Qmetrics Technologies

Jeffrey J. Bazarian  
University of Rochester School of Medicine and Dentistry

Mark H. Mirabelli  
University of Rochester School of Medicine and Dentistry

Katherine H. Rizzone  
University of Rochester School of Medicine and Dentistry

Heather M. Ma  
University of Rochester School of Medicine and Dentistry

Peter Rosella  
University of Rochester School of Medicine and Dentistry

Saara Totterman  
Qmetrics Technologies

Edward Schreyer  
Qmetrics Technologies

Jose G. Tamez-Pena  
School of Medicine and Health Sciences, Tecnologico de Monterey, Mexico

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Abstract

Background

Diffusion Tensor Imaging (DTI) has shown measurable changes in the brains of patients with persistent post-concussive syndrome (PCS). Because of inconsistent results in univariate DTI metrics among patients with mild traumatic brain injury (mTBI), currently, there is no single objective and reliable MRI index for the clinical decision-making for patients with PCS.

Objectives

The aim of this study was to evaluate the performance of a newly developed post-concussive syndrome index (PCSI) derived from machine learning of multiparametric MRI data, to classify and differentiate subjects with mTBI and PCS history from those without history of mTBI.

Methods

Data were retrospectively extracted from 139 patients aged between 18 and 60 years with PCS who had MRI examinations obtained 2 weeks to 1-year post-mTBI, as well as MRI data from 333 subjects without a history of head trauma. The performance of the PCSI was assessed by comparing patients with a clinical diagnosis of PCS to control subjects. The PCSI values for patients with PCS were compared based on mechanism of injury, time interval from injury to MRI examination, gender, prior concussion history, loss of consciousness, and reported symptoms.

Results

Patients with mTBI had a mean PCSI value of 0.57, compared to the control group, which had a mean PCSI value of 0.12 ($p = 8.42 \times 10^{-23}$) with accuracy of 88%, sensitivity of 64%, and specificity of 95% respectively. No statistically significant differences were found in PCSI values when comparing by mechanism of injury, gender, or loss of consciousness.

Conclusion

The PCSI for individuals aged between 18 and 60 years was able to accurately identify patients with post-concussive injuries from 2 weeks to 1-year post-mTBI and differentiate them from controls. The study's results suggest that the multiparametric MRI-based PCSI has great potential as an objective clinical tool to support the diagnosis, treatment, and follow-up care of those with post-concussive syndrome. Future research is required to investigate the replicability of this method using other types of clinical MRI scanners.

1 Introduction
Traumatic brain injuries (TBI) are evaluated based on clinical symptoms, neurological impairment, and imaging findings [1–5]. The majority (80–90%) of TBIs are mild, characterized by Glasgow Coma Scale scores of 13–15 [5–7]. Mild TBI and concussion are often used interchangeably, with sports-related concussions being a subtype [6,8]. It is estimated that 1.4–3.8 million concussions occur annually in the US, caused by sports, recreational activities, falls, assaults, and motor vehicle accidents [1,2,4,5].

Symptoms associated with concussions include headaches, amnesia, dizziness, fatigue, drowsiness, sleep disturbance, irritability, blurred vision, nausea, hypersensitivity to light and noise, emotional lability, anxiety, depression, deficits in attention, concentration, memory, executive function, balance problems, and/or loss of consciousness for less than 30 minutes [5,7–14]. Loss of consciousness occurs in 10–20% of concussions but is not required for diagnosis [15–17]. Most symptoms resolve within 14 days in adults and 4–6 weeks in children [4,6,7,16–18]. However, 15–30% of mTBI patients may experience post-concussion symptoms, referred to as persistent post-concussive syndrome, for several months or longer [4,6,7,17–20]. In the Prospective TRACK-TBI study, 33% of patients were functionally impaired 3 months after injury, 22.4% were not at full functional status 1 year after injury [4] and some patients with mTBI may experience long-term disability [7]. Schneider et al reported that a poor 1-year cognitive outcome was reported in 13.5% of patients with mTBI [21].

In most post-acute patients with a history of mTBI and post-concussive syndrome, there is no radiological evidence of brain injury using CT and conventional MRI techniques [4,5,7,18,22]. Recently, an advanced MRI technique DTI has been used to evaluate mild traumatic injuries in the acute, subacute, and delayed phases [5,7,18]. However, literature reviews have found variable, inconsistent, or negative findings in diffusion metrics between patients with post-concussive syndrome and controls [5,6,18,22]. Additionally, consistent diffusion imaging abnormalities were not found in patients with post-concussive syndrome and behavioral changes [18]. The inconsistencies in group differences in the locations of DTI-related white matter abnormalities have been proposed to be related to the heterogeneous nature and symptoms of mTBI, different mechanisms of injury, variable locations and phases of injury, differences in DTI protocols, and/or limited numbers of control and subject populations [5,18,23]. Previous studies using DTI to evaluate PCS at the group level have focused on univariate analyses of diffusion metrics, such as fractional anisotropy (FA), apparent diffusion coefficient (ADC), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) [24]. Although microstructural changes in DTI metrics have been demonstrated at a group level in patients with PCS, the practical application of these changes at an individual level for diagnosis, treatment, and follow-up care has been lacking [18,25].

Despite the advances in measuring changes in the brain related to traumatic brain injury, there is currently no objective and reliable MRI assessment to guide clinical decision-making for individual patients with mTBI and PCS [18,25,26]. The lack of objective data about mTBI in patients leads to challenges in both the diagnosis, prognosis, and treatment of patients with a history of mTBI and post-concussive syndrome, based on subjective symptom reports and clinical examinations [25]. To address this issue, machine
learning approaches have been suggested. Machine learning has also been applied to MRI data in patients with traumatic brain injuries. For example, Mitra et al. used a machine learning technique to classify patients with a history of mild, moderate, or severe TBI based on altered structural connectivity patterns within intra- and inter-hemispheric white matter pathways secondary to trauma. Additionally, Goswami et al. reported that for retired football players with a history of multiple concussions, machine learning of mean and radial diffusion data showed alterations involving the uncinate fasciculus, which is associated with behavioral regulation. Vergara et al. reported that data from resting state functional magnetic resonance imaging (fMRI) used to assess network connectivity was more accurate than DTI in detecting mild traumatic brain injury at a group level. Luo et al. reported that a support vector machine algorithm of multiparametric fMRI data in patients with mild traumatic brain injury could improve the classification performance of mTBI compared to normal controls by using the brain regions associated with emotion and cognition. Liu et al. reported that an algorithm developed from multi-feature analysis of data from diffusion-weighted imaging, fMRI, and volumetrics may aid in the classification of patients with mTBI compared with controls. Abdelrahman et al. reported that combining multiple DTI metrics improved the accuracy of identifying patients with chronic moderate brain injury, with mean time since injury = 9 years, compared to controls.

Machine learning (ML) has also been widely applied to multiparametric clinical MRI data in oncology and other medical conditions. The purpose of using machine learning has been reported to develop clinical tools that support diagnoses, predict prognoses, and predict responses to treatment for different diseases and medical conditions. In our previous work, we developed a PCSI for patients with a history of mTBI using a feature selection process applied to multiparametric structural and diffusion MRI data. The PCSI combined complex radiomic information from the magnetization prepared - rapid gradient echo (MP-RAGE) series, FA and ADC series. This method enabled the detection of post-concussive imaging changes in all series, even when no apparent findings were evident on the clinical MRI examinations.

The objective of this study is to evaluate the performance of a multiparametric MRI-based PCS Index in classifying subjects with and without a diagnosis of concussion with persisting post-concussion symptoms and exploring the associations with gender, mechanism of injury, elapsed time from injury, prior concussion history, and clinical symptoms in patients aged 18–60.

2 Material and Methods

2.1 Participants

The Research Subjects Review Board of the University of Rochester approved this retrospective observational analysis. Figure 1 shows the inclusion-exclusion criteria for this retrospective review of the medical records of patients referred to an outpatient MRI center from 2016 to 2022. MRI imaging was done for uninjured patients ranging in age from 18 to 60 years who were referred for MRI because of
subjective complaints of headaches, hearing loss, or other complaints and who had normal MRI examinations. Retrospective review was also done for the medical records from 2016 to 2022 for patients ranging in age from 18 to 60 years who were referred for MRI at the same facility by Sports Medicine Physicians, Physical Medicine, and Rehabilitation Physicians, or Neurologists for evaluation of head trauma. Inclusion criteria included a clinical diagnosis of concussion with persistent PCS and MRI performed at least 2 weeks and no later than 12 months after mTBI, while exclusion criteria included dental braces, prior brain surgery, ventricular shunts, intracranial hemorrhage, intra-axial MRI signal abnormalities, skull fractures, or standard contraindications for MR imaging. Patient age and gender, number of previous concussions, presence of absence of loss of consciousness (LOC) at the most recent concussion, the time between injury and MRI, and persistent signs and symptoms were extracted from the electronic medical records. All patient identifiers were removed before the analyses.

2.2 IMAGE ACQUISITION

All MRI exams for the concussed patients and 27 student athlete controls were performed between 2016, and 2022, on one of two 3T Siemens Skyra MRI Scanners using a 20-channel Head/Neck Coil using the following imaging protocol: Sagittal T1-FLAIR images (FOV = 220 mm, 25 slices; 4 mm thick, TR = 2000 ms, TE = 9 ms, TI = 900 ms, 2 averages), T1- weighted MP-RAGE images (FOV = 250 mm, 208 axial slices; 1x1x1 mm, TR = 1,200 ms, TE = 2.29 ms, TI = 600 ms), Flip angle = 8 degrees, 3D axial SWI images (FOV 220 mm, 88 slices/1.5 mm slice thickness (interleaved)/ TR 27 ms, TE 29 ms, 1 average), DOUBLE IR (FLAIR)- Fat-sat FLAIR images (FOV 260 mm, 120 slices, 1.4 mm slice thickness, TR 7,500 ms, TE 321 ms, TI 1: 3,000 ms; TI 2: 450 ms, 1 average, Acceleration factor 2, ref lines 24, Turbo Factor 256). DTI acquisition parameters were axial DTI/ TA: 10:14 min, FOV 256 mm, 70 slices, 2 mm slice thickness, TR 9,000 ms, TE 88 ms, Flip Angle 15°, 1 average, Acceleration Factor 2/ref lines 24, Diffusion directions 64, b-value 1: 0 s/mm²; b-value 2: 1,000 s/mm2 GRE Field Mapping for geometric and eddy current corrections 86 slices, FOV 256 mm, 2 mm slice thickness, TR 838 ms, TE1: 4.92 sec, TE2: 7.38 ms, Flip angle: 60°. Diffusion images were also corrected for susceptibility distortions with the acquisition of a sequence with 64 PA reversed phase directions.

For the other control patients (n = 306) Sagittal T1-FLAIR (FOV = 220 mm, 25 slices; 4 mm thick, TR = 2000 ms, TE = 9 ms, TI = 900 ms, 2 averages), T1- MP-RAGE (208 slices; 1x1x1 mm, TR = 1,200 ms, TE = 2.29 ms, TI = 600 ms), FOV = 250 mm, Flip angle = 8 degrees, and 3D axial SWI (88 slices/1.5 mm slice thickness (interleaved)/FOV 220 mm, TR 27 ms, TE 29 ms, 1 average). Also acquired were axial T2 FLAIR images through the head: (FOV = 220 mm, 30 slices; 4 mm thick, TR = 9000 ms, TE = 94 ms, TI = 2500 ms, 2 averages), and axial fat-suppressed T2WI images (FOV = 180 mm 24 slices; 2.5 mm thick, TR = 3640 ms, TE = 77 ms, 3 averages) through the posterior cranial fossa for control patients with subjective hearing loss or headaches. For those with subjective hearing loss, axial 3D Constructive Interference Steady State (CISS) images were also obtained through the posterior cranial fossa (FOV = 160 mm, 60 slices; 0.6 mm x 0.6 x 0.6 mm, TR = 8.05 ms, TE = 3.75 ms, 1 average). DTI acquisition parameters for the
control subjects were identical to those described above. All image sets in this study were correlated with clinical data and anonymized.

2.3 Image Analysis

2.3.1 Image Preprocessing, Segmentation, and Quantification

In each subject, 3 MRI series (MP-RAGE, Apparent Diffusion Coefficient, and Fractional Anisotropy) were combined, then segmented into 2 tissue types (gray and white matter) in 8 anatomical subregions using a derivative of the 152c Montreal Brain atlas. These subregions include right and left temporal, occipital, parietal and frontal lobes. Five radiomic quantifications were performed, including raw signal measurement, fractal signature, and three-level wavelet decompositions which provided information about the three-dimensional texture patterns of the measurements. The two tissues, 3 MRI series, 8 subregions, and five radiometric measurements yielded 240 numeric sets, each further described by 33 statistical descriptions ranging from simple arithmetic mean and standard deviation to complex representations of numeric distribution yielding a total set of 7920 individual quantitative values for each subject. Logistic Regression with L1 regularization was used to estimate the subset of features of the Post-Concussive Syndrome Index (PCS Index) [35]. The index produces a value between 0 and 1 for each subject, with values less than 0.5 regarded as consistent with uninjured healthy subjects and values of 0.5 or greater associated with post-concussive subjects. Details of image processing and Machine Learning are provided in Tamez-Pena, et.al [27]. All image processing was done using CIPAS (Qmetrics Technologies, Rochester, NY), and prediction of the PCS Index was carried out using R 4.1.2 with the FRESA.CAD 3.3.1 Package [36].

2.4 Statistical Analysis

For each participant, we recorded the PCS Index, gender, age, weight, health, the origin of trauma or condition, and clinical symptoms at the time of MRI. Age, weight, height, and PCS Index of subjects in the validation set were described by mean, and standard deviation, and stratified by cases and controls. Statistical differences between cases and controls were computed using a t-test for age, height, and weight. PCS Index was described by receiver operating characteristics (ROC) and the receiver operating characteristic area under the curve (ROCAUC). The paper also reports the accuracy, sensitivity, specificity, and diagnostic odds ratio between concussed and non-concussed subjects with their corresponding confidence intervals. The behavior of PCS Index values for control group subsets (uninjured subjects with hearing loss, headaches, other indications, or young athletes) was described by frequency and PCS Index association using violin plots and compared using ROC analysis. Injured subjects’ PCS Index values were compared by gender, loss of consciousness at the time of injury, mechanism of injury (sports, vehicular injuries, and assaults/falls), the time interval from injury to MRI examination, prior concussion history and reported symptoms. The significant associations to binary symptoms were computed using a
Wilcoxon signed-rank test, and the effect size was described by ROCAUC. None of the p-values were adjusted for multiple comparisons. All statistical analyses were carried out using R 4.2.2.

3 RESULTS

Table 1: Demographics of the PCSI Validation Cohort

<table>
<thead>
<tr>
<th></th>
<th>All (n=333)</th>
<th>Control (n=264)</th>
<th>Case (n=69)</th>
<th>Females (n=132)</th>
<th>Males (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender Distribution</strong></td>
<td>(F/M/N)</td>
<td>(F/M/N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>150/113/1</td>
<td>39/30</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>MRI Indication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hear Loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>132</td>
<td>88</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trauma Origin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sports</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVA</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>42.7(11.2)</td>
<td>31.9(14.3)**</td>
<td>41.6(11.0)</td>
<td>33.1(14.7)**</td>
<td>44.4(11.2)**</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>170.1(10.4)</td>
<td>170.7(10.9)</td>
<td>163.7(7.3)</td>
<td>164.6(7.7)</td>
<td>178.4(7.6)</td>
</tr>
<tr>
<td><strong>Weight (Kg)</strong></td>
<td>90.3(25.3)</td>
<td>77.3(20.7)**</td>
<td>82.7(23.7)</td>
<td>71.6(19.9)**</td>
<td>100.7(23.7)</td>
</tr>
<tr>
<td><strong>PCS Index</strong></td>
<td>0.12(0.17)</td>
<td>0.57(0.34)**</td>
<td>0.13(0.19)</td>
<td>0.57(0.37)**</td>
<td>0.10(0.14)***</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01, ***p<0.001

Table 1 shows the demographics of the study participants. The MRI indication of the control/uninjured participants was hearing loss (n=132), followed by headache (n=88) and several other conditions (n=42). The mechanism of injury of the control/PCS participants was sports related (n=34), motor vehicle (n=14), or other causes (n=21). The gender distribution of the case/control sets was statistically different, where female participants were more common in the control group. There were marked differences between the age of injury of participants (Cases) and normal clinical patients (Controls). Controls were slightly older (42.7 ± 11.2) than cases (31.9 ± 14.3 years). Another significant difference in this cohort was the weight of the control participants were heavier than cases (90.3 ±25.3 vs. 77.3 ±20.7, p<0.001).

Regarding the PCS Index, Figure 2 shows the distribution of the index across all patients and stratified by gender. The Index could separate PCS subjects from non-injury subjects with an accuracy of 0.88 (95%CI [0.84,0.92]), sensitivity of 0.64 (95%CI [0.51,0.75]), specificity of 0.95 (95%CI [0.91,0.97]), diagnostic odds ratio (DOR) of 31 (95%CI [15,65]), and ROCAUC of 0.87 (95%CI [0.82,0.92]). The performance of the index was similar between males and females where sensitivity, specificity, and DOR were 0.63, 0.97, and 63 vs. 0.64, 0.93, and 23 for males and females respectively.

Because there was a strong age imbalance between cases and controls, we tested the hypothesis that the index was not associated with the participant’s age. The test consisted of modeling the PCS Index by
participant age-adjusted by subject class (Case or Control). The result of the model indicated that the subject class predicted most of the variance of the PCS Index ($p<0.001$), while age did not ($p=0.42$). Hence, the PCS index is not affected by participant age.

Table 2: Symptoms and PCSI. **Bold** values indicate ROC AUC greater than 0.6.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
<th>Mean Index Present</th>
<th>Mean Index Absent</th>
<th>ROCAUC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases (n=43)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>60 (87%)</td>
<td>0.567</td>
<td>0.572</td>
<td>0.50</td>
</tr>
<tr>
<td>Concentration</td>
<td>43 (62%)</td>
<td>0.604</td>
<td>0.507</td>
<td>0.59</td>
</tr>
<tr>
<td>Photophobia</td>
<td>39 (57%)</td>
<td>0.535</td>
<td>0.610</td>
<td>0.43</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35 (51%)</td>
<td>0.593</td>
<td>0.542</td>
<td>0.56</td>
</tr>
<tr>
<td>Sleep</td>
<td>35 (51%)</td>
<td>0.584</td>
<td>0.551</td>
<td>0.53</td>
</tr>
<tr>
<td>Dizziness</td>
<td>34 (49%)</td>
<td>0.550</td>
<td>0.585</td>
<td>0.46</td>
</tr>
<tr>
<td>Memory Problems</td>
<td>34 (49%)</td>
<td>0.528</td>
<td>0.606</td>
<td>0.44</td>
</tr>
<tr>
<td>Mood Problems</td>
<td>33 (48%)</td>
<td>0.572</td>
<td>0.564</td>
<td>0.49</td>
</tr>
<tr>
<td>Noise Sensitivity</td>
<td>33 (48%)</td>
<td>0.532</td>
<td>0.600</td>
<td>0.44</td>
</tr>
<tr>
<td>Vision Problems</td>
<td>32 (46%)</td>
<td>0.671</td>
<td>0.478</td>
<td><strong>0.66</strong>*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>31 (45%)</td>
<td>0.633</td>
<td>0.514</td>
<td>0.60</td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (45%)</td>
<td>0.594</td>
<td>0.546</td>
<td>0.55</td>
</tr>
<tr>
<td>Irritability</td>
<td>28 (41%)</td>
<td>0.543</td>
<td>0.585</td>
<td>0.54</td>
</tr>
<tr>
<td>Neck Pain</td>
<td>24 (35%)</td>
<td>0.440</td>
<td>0.636</td>
<td><strong>0.34</strong>*</td>
</tr>
<tr>
<td>Balance</td>
<td>21 (30%)</td>
<td>0.489</td>
<td>0.602</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Controls (n=162)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>132 (50%)</td>
<td>0.118</td>
<td>0.100</td>
<td>0.50</td>
</tr>
<tr>
<td>Headache</td>
<td>88 (34%)</td>
<td>0.143</td>
<td>0.094</td>
<td>0.54</td>
</tr>
<tr>
<td>Other</td>
<td>42 (16%)</td>
<td>0.147</td>
<td>0.121</td>
<td>0.44</td>
</tr>
</tbody>
</table>

* $p<0.1$

3.1 Exploratory Analysis of the PCS Index
Table 2 shows the distribution of the most common PCS symptoms and their association with the PCS Index. The most common symptom of PCS patients was headache (87%) followed by concentration issues (62%). Headache was not associated with the index value, but the presence of vision problems was associated with a higher index value (0.671 vs. 0.478, p(P>A) = 0.02). Concentration problems and anxiety showed a trend (p(P>A) < 0.1) of higher index value when the symptom was present. Both symptoms had a ROCAUC of 0.6. Figure 3 shows the distribution of the PCS Index for the three top symptoms, as well as the distribution of the PCS Index and the presence of Neck pain. The neck pain results showed a negative trend of having a lower index value for subjects reporting neck pain vs. patients without neck pain (P=0.440, A=0.636, p(P<A)=0.03).

Figure 4 shows the distribution of the PCS Index concerning the history of previous concussions, loss of consciousness, and the mechanism of trauma. We observed in all these cases that there was a positive trend toward a higher PCS Index value on the three exploratory analyses, but none of them reached statistical significance (p>0.1).

We also explored the effect of elapsed time from injury on the PCS Index, observing a non-significant trend of diminishing index values with increasing time from injury (p=0.12).

The final exploratory analysis was the exploration of the behavior of the index in the non-trauma participants. The results are shown at the bottom of Table 2. The hearing loss, headache, and other patient sub-cohorts had non-significantly different PCSI values than the other non-trauma patients (p(A≠B) = 0.16, 0.88 and 0.09, respectively).

### 4 DISCUSSION

This study showed that our previously developed machine-learning-based classifier, the Post-Concussion Syndrome Index, enabled accurate identification and differentiation of patients with persistent post-concussive syndrome from subjects without concussion with high accuracy [27]. In this study, we further evaluated the performance of the PCSI model by classifying a new set of patients with post-concussive syndrome and comparing them to non-concussed subjects aged between 18 and 60. The results of this study indicate that the PCSI performed well in the new population, with a mean PCSI value of 0.57 for patients with post-concussive syndrome and a mean PCSI value of 0.12 for control subjects (ROCAUC 0.87, 95%CI [0.84,0.92]). The PCSI had a sensitivity of 64%, specificity of 95%, and accuracy of 88% in the evaluation of patients with post-concussive syndrome. Clear differences in the PCS Indices between controls and injured patients were observed in population subgroups, including females, males, sports-related MTBI, and non-sports-related mTBI, as well as sub-cohorts of injured and non-injured athletes. These results suggest that mTBI subjects with PCS exhibit significant differences in the behavior of the MRI signal from combined structural and DTI image data when compared to control subjects.

No significant differences were found in the PCS Indices based on gender for the control group or the mTBI cohort, consistent with previously reported inconsistent results regarding the effect of gender on the
frequency of PCS and the rate of clinical recovery. The analysis of the PCS Index showed a non-statistically significant, slightly downward trend associated with increased time intervals between injury and MRI. These findings are similar to multiple prior studies which showed persistent, although inconsistent, changes in individual DTI metrics over weeks to months after mTBI. These observations are consistent with previous findings of partial resolution of alterations in AD and MD in cerebral white tracts from 2 weeks to 6 months post-mTBI, compared to persistent changes in lower FA. Contradictory results have been reported regarding the outcome of patients with PCS related to the number of prior concussions. In our study, the relationship between the number of prior concussions and the PCS Index showed a trend of increasing PCS Index values for subjects with a history of more prior concussions, however, this did not reach statistical significance. In our study, no statistically significant differences were found in the PCS Indices when comparing sub-cohorts of injured subjects who lost consciousness at the time of injury and those who did not, consistent with previous reports that loss of consciousness is not associated with increased rate and duration of PCS.

The exploratory analysis of case subjects revealed that certain symptoms are associated with higher PCS Index values. Specifically, we found that subjects with vision problems had higher PCS Index values than those without. Similar trends were found for anxiety and concentration problems. As illustrated in Figure 3, subjects reporting vision problems including blurring had higher index values than those who did not. All patients with vision problems either complained about binocular blurred vision or had convergence insufficiency upon examination. At least, 12 of the 30 subjects with vision problems also reported LOC after the concussive episode. Unfortunately, a complete ophthalmologic report was unavailable for these subjects; therefore, our ability to localize the potential injury site is limited. However, blurred vision is often the result of diplopia or nystagmus, which can occur from a dysfunction in pathways located in the midbrain, a region with known biomechanical vulnerability to concussive forces. The connection between these symptoms and midbrain dysfunction is more likely for the subset of subjects presenting with both blurred vision and LOC, pointing to midbrain-thalami involvement.

It’s worth noting that the multiparametric index was negatively correlated with the presence of neck pain, which suggests the possibility of PCS symptoms originating from neck injury rather than structural brain microtrauma.

The main limitation of this study is the lack of longitudinal observations, thus the results presented in this study do not conclusively indicate whether the multiparametric Index can predict the resolution of PCS or whether the brain changes observed due to mTBI are permanent fixtures on affected patients. Furthermore, the presented results were validated using the same hardware, obtained using the same protocol on the same types of 3.0 Tesla MRI scanners, thus enabling data harmonization. Therefore, the performance of the developed PCS Index must be evaluated on other types of MRI scanners, such as 3 or 1.5 Tesla, and with other diffusion tensor imaging protocols.

6 SUMMARY and CONCLUSIONS
The results of this study show that the previously developed PCS Index applied to multiparametric MR image data from individuals aged between 18 and 60 years can accurately classify and differentiate patients with post-concussive syndrome from controls from 2 weeks to 1 year after mTBI with high sensitivity, specificity, and accuracy. No statistically significant differences were found in the PCS Indices when comparing by gender or by loss of consciousness at the time of injury and those who did not. The study's results suggest that the PCS Index has great potential as an objective clinical tool to support the diagnosis, treatment, and follow-up care of those with post-concussive syndrome. Future research is required to investigate the replicability of this method using other types of clinical MRI scanners.

**Abbreviations**

AD  Axial Diffusivity  
ADC  Apparent Diffusion Coefficient  
DOR  Diagnostic Odds Ratio  
DTI  Diffusion Tensor Imaging  
FA  Fractional Anisotropy  
fMRI  Functional Magnetic Resonance Imaging  
LOC  Loss of Consciousness  
MD  Mean Diffusivity  
ML  Machine Learning  
MP-RAGE  Magnetization Prepared - RApid Gradient Echo  
mTBI  Mild Traumatic Brain Injury  
PCS  Post-Concussive Syndrome  
PCSI  Post-Concussive Syndrome Index  
RD  Radial Diffusivity  
ROC  Receiver Operating Characteristics  
ROCAUC  Receiver Operating Characteristics Area Under the Curve  
TBI  Traumatic Brain Injuries
Declarations

Ethics Approval and Consent to Participate

This study was approved by the institutional review board of the University of Rochester School of Medicine and Dentistry.

Consent for Publication

The data were obtained from patient clinical records with removal of patient identification data. Therefore, no individual person’s data was disclosed and consent was not needed, per IRB.

Availability of Data and Material

The data was obtained from patient clinical records with removal of patient identification data.

The data that support the findings of this study are available from Qmetrics, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Qmetrics.

Competing Interests

- Authors Jose Tamez-Peña, Saara Totterman, Edward Schreyer and Patricia Gonzalez have equity interest in Qmetrics Technologies.

- Authors Edward Schreyer and Patricia Gonzalez receive employment-related compensation from Qmetrics Technologies. Qmetrics Technologies may provide future image analysis products or services related to the content of this study.

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Authors’ Contributions

- All authors contributed to the study conception and design.

- Material preparation, data collection and analysis were performed by Steven P. Meyers, Jose Tamez-Peña, Edward Schreyer, Patricia Gonzalez and Saara Totterman.

- The first draft of the manuscript was written by Steven P Meyers and all authors commented on previous versions of the manuscript.

- All authors read and approved the final manuscript.
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References


**Figures**
**Figure 1**

Inclusion-Exclusion Criteria for the study participants. This paper presents the performance of the PCSI on the validation participants.
Figure 2

Distribution of the PCSI. Top left, violin plots of the Cases and Controls stratified by Gender. Top right, ROC plot of all subjects. Bottom plots, ROC plots of Males and Females.
Figure 3

Violin plots of the distributions of the PCSI based on the case symptoms. Subjects reporting vision problems had PCSI values larger than subjects without problems (p=0.02). Subjects reporting neck pain had lower PSCI values than subjects without neck pain (p=0.03). The other symptoms had non-significant differences between the presence or absence of symptoms.
Figure 4

Violin plots showing the distribution of case subjects according to the history/origin of the concussion. Left, distribution based on the number of concussions. Middle, PCSI distribution according to the history of loss of consciousness. Right, differences between the origin of the trauma: Sports injury or another traumatic event.